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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,390	05/31/2006	Annick Harel-Bellan	BDM-06-1098	4465

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,390	HAREL-BELLAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *5-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/19/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claims 1-11, in the reply filed on 04/04/2007 is acknowledged.

Status of the Application

Claims 1-14 are pending. Claims 1-4 are currently under examination. Claims 12-14 are withdrawn as being drawn to a non-elected invention. Claims 5-11 will not be examined because they are objected to for not being in proper form as discussed below.

Claim Objections

Claims 5-11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 5-11 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing the activity of RNAi in cells *in vitro* by delivering to said cells a TAT protein and a nucleic acid

comprising a sense and antisense sense sequence, does not reasonably provide enablement for a method of inducing the activity of RNAi in cells *in vivo* by delivering to said cells a TAT protein and a nucleic acid comprising a sense and antisense sense sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a method of inducing the activity of RNAi in any cell, *in vitro* and *in vivo,* by delivering to said cells a TAT protein and a nucleic acid comprising a sense and antisense sense sequence.

The specification as filed discloses inhibition of Green Fluorescent Protein (GFP) in cells comprising transfecting COS-7 cells in vitro with a vector expressing a siRNA comprising a TAR sequence and cultivating the cells with a TAT protein (see Example 2). The specification does not teach a process for delivering any siRNA comprising a TAR sequence to any cell or tissue of any specie *in vivo* that is capable of inducing the activity of RNAi in said cell or tissue of any specie *in vivo*.

There is no guidance in the specification as filed that teaches how to target the claimed siRNA to cells or tissues *in vivo* or inhibit the expression of specific target endogenous genes of cells or tissues *in vivo*. Although the specification discloses inhibition of a GFP gene expression in one mammalian cell type using a siRNA transfected into such cells, such a disclosure would not be considered enabling since the state of antisense and RNAi-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 1-4 encompass a method of inducing the activity of RNAi in any cell or tissue of any specie *in vivo* by delivering to said cells or tissues a TAT protein and a nucleic acid comprising a sense and antisense sense sequence. Although the specification discloses inhibition of Green Fluorescent Protein (GFP) in cells comprising transfecting COS-7 cells in vitro with a vector expressing a siRNA comprising a TAR sequence and cultivating the cells with a TAT protein, this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense and RNAi. Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more

problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2). The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).

The state of the art for therapeutic *in vivo* applications for RNAi face similar hurdles as antisense as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles. However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Although RNAi has been seen as the new magic bullet to silence genes, "...magic bullets need magic guns" (stated by William Pardridge as quoted by Adams in The Scientist (2005) Vol.19:Issue1). Adams notes that researchers have struggled to get their therapies to particular targets and as stated by McCaffrey "[t]heir approach involves injecting large amounts of virus [vectors expressing shRNA] into the tail vein of mice, or into an artery leading to the liver. Its efficient but probably isn't going to work for humans" (see page 2 The Scientist (2005) Vol.19:Issue1). Even some of the applicants of the instant application have noted the unpredictability of using siRNA injected into the vein and observes that "[i]n some cells, inhibition seemed nearly complete, whereas in others, low or moderate levels of EGFP were observed....These results may be due to incomplete inhibition in cells that take up lesser amounts of siRNA. High

pressure delivery of fluorescently labeled siRNA reveals that in vivo uptake is not equal in all hepatocytes when this method is used' (Lewis et al. Nature Genetics 2002 Vol.32;107-108).

As outlined above, it is well known that there is a high level of unpredictability in the antisense and RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibiting expression of a target endogenous gene *in vivo* by delivering polynucleotides to cells via injection into vessels. Delivery and inhibition of a Green Fluorescent Protein (GFP) in cells comprising transfecting COS-7 cells in vitro with a vector expressing a siRNA comprising a TAR sequence and cultivating the cells with a TAT protein does not correlate with the ability to inhibit any endogenous gene expressed in any cell or tissue of any specie *in vivo*.

While one skilled in the art may be able to produce a siRNA comprising a TAR sequence targeted to a GFP gene and induce expression in mammalian COS-7 cells, the specification as filed does not teach a method of inducing RNAi comprising a TAR sequence and cultivating the cells with a TAT protein such that inhibition of expression results in any cell or tissue of any specie *in vivo*.

In view of the unpredictability in the art of antisense and RNAi-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of any siRNA *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of an endogenous gene in cell or tissue. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the siRNA *in vivo*, delivery of the siRNA to cells or tissue, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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KC
Examiner
Art Unit 1635

/Sean McGarry/
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